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EXAMINER

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ART UNIT PAPER NUMBER

1636

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/28/2005 has been entered.

Receipt is acknowledged of an amendment, filed 11/28/2005, in which claims 1-24 and 47-48 were canceled. Receipt is also acknowledged of an amendment, filed 1/9/2006, in which claims 50 and 51 were amended, and claims 52-57 were newly added. Currently, claims 25-46 and 49-57 are pending.

Any rejection of record in the previous office actions not addressed herein is withdrawn.

Election/Restrictions

Applicant elected Group II (claims 31-34) and SEQ ID NO: 32 with traverse in the reply filed on 12/29/2004. Currently, claims 31-34 and 49-57 read on the elected group.

Claims 25-30 and 35-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/29/2004.

Currently, claims 31-34 and 49-57 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 1/3/2006, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Objections

Claims 33, 34 and 52-57 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 33 is objected to as failing to further limit the subject matter of claim 32. Claim 32 is drawn to an isolated peptide comprising the amino acid sequence of SEQ ID NO: 32. Claim 33 is broader in scope in that it is drawn to peptides comprising at least a 10 contiguous amino acid segment of the isolated amino acid sequence of claim 32, wherein said contiguous amino acid segment comprises at least one contiguous amino acid from amino acids 37-117 of SEQ ID NO: 32. The genus of peptides of at least 10 amino acids encompassed by claim 33 is broader in scope than the peptide comprising the entire sequence of SEQ ID NO: 32. As such, art could potentially be applied to claim 33 that would not anticipate claim 32.

Claims 34 and 52-57 depend from claim 33 and are objected to for the same reasons as set forth above for claim 33.

Claim 55 is objected to as failing to further limit the subject matter of claim 52. Claim 55 is drawn to an isolated peptide consisting of amino acids 24-45 of SEQ ID NO: 32. However, claim 52 is drawn to a peptide consisting of amino acids 24-52 of SEQ ID NO: 32. A peptide

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that consists of a particular amino acid sequence cannot be further limited to a different amino acid sequence.

Claims 56 and 57 depend from claim 55 and are objected to for the same reasons as set forth above for claim 55.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.** This rejection was made in the Office action mailed 8/25/2005 and has been altered to address Applicant's remarks.

Claims 33 and 34 are drawn to an isolated peptide comprising at least a 10 contiguous amino acid segment, or a 10-20 contiguous amino acid segment, of the isolated amino acid sequence of SEQ ID NO: 32, wherein the contiguous amino acid segment comprises at least one contiguous amino acid from amino acids 37-117 of SEQ ID NO: 32.

The specification envisions fragments of 10 contiguous amino acid residues or at least 10-20 contiguous amino acid residues (e.g. paragraph bridging pages 49-50). The reply filed on 11/28/2005 asserts that support for the amendment can be found at page 22, lines 19-23 and Table

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1. At page 22, lines 19-23 the specification defines fragments of SEQ ID NO: 11 to include the regions which contain the variation in nucleotides between the variant and the original sequences. SEQ ID NO: 11 encodes SEQ ID NO: 32. The description provided in Table 1 for SEQ ID NO: 32 indicates that SEQ ID NO: 32 differs from wild-type ghrelin in that it has “[a]lternative 70 amino acids from position 35 in the wild type protein creating a variant with 117 amino acids.” Thus, the specification provides support for fragments containing at least one contiguous amino acid from amino acids 35-104 of SEQ ID NO: 32. Table 1 indicates that ghrelin variant 2 has alternative 70 amino acids from position 35 in the wild type protein.

The specification does not provide support for protein fragments that comprise at least one contiguous amino acid from amino acids 37-117 of SEQ ID NO: 32. Therefore, claims 33 and 34 are a departure from the specification and claims as originally filed.

Claims 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The claims are drawn to an isolated amino acid sequence coded by nucleotides 112-462 of SEQ ID NO: 11, wherein the amino acid at position number 26 of SEQ ID NO: 32 is acylated (claim 50) or octanoylated (claim 51).

The reply filed on 10/28/2005 asserts that support for this amendment can be found at page 24, lines 1-9. This passage of the specification teaches that the disclosed proteins may be

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modified by natural processes such as post-translational modifications. The post-translational modifications contemplated by the present specification include acylation. The modifications do not include octanoylation. Further, the reply filed on 1/9/2006 points to the teachings of Kojima et al (Nature, Vol. 402, pages 656-60, 1999, cited on the IDS filed 1/3/2006) for support for the acylation at position 26, which is asserted to correspond to the acylation site of the amino acid at position 3 of processed, wild-type ghrelin.

While, the specification provides support for acylation of the disclosed proteins, the specification does not literally or inherently describe the acylation of the amino acid at position number 26 of SEQ ID NO: 32. The specification does not describe the octanoylation of any protein, and thus does not describe the octanoylation of position number 26 of SEQ ID NO: 32. The recognition that wild-type ghrelin is acylated at position 3 of the processed protein does not provide support for the acylation of Applicant's novel protein. The specification does not recognize that the variant Ghrelin of SEQ ID NO: 32 is processed in the same manner as wild-type ghrelin and is acylated at the same position.

Therefore, claims 50 and 51 are a departure from the specification and claims as originally filed.

Claims 52-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

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Claims 52-54 are drawn to an isolated peptide consisting of amino acids 24-52 of SEQ ID NO: 32. Claim 53 requires the amino acid at position number 26 of SEQ ID NO: 32 to be acylated. Claim 54 requires the amino acid at position number 26 to be octanoylated.

The reply filed on 1/9/2006 asserts that support for the amendment can be found at page 22, lines 19-27 and page 24, lines 1-9. However, these passages do not provide support for the claimed invention. While the specification provides support for a genus of fragments containing at least 10 amino acids and containing at least one contiguous amino acid from amino acids 35-117 of SEQ ID NO: 32, the specification does not specifically disclose a fragment consisting of amino acids 24-52 of SEQ ID NO: 32. Further, the specification provides support for post-translational modifications such as acylation, the specification does not literally or inherently describe the acylation of the amino acid at position number 26 of SEQ ID NO: 32. The specification does not describe the octanoylation of any protein, and thus does not describe the octanoylation of position number 26 of SEQ ID NO: 32.

Therefore, claims 52-54 are a departure from the specification and claims as originally filed.

Claims 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 55-57 are drawn to an isolated peptide consisting of amino acids 24-45 of SEQ ID NO: 32. Claim 56 requires the amino acid at position number 26 of SEQ ID NO: 32 to be acylated. Claim 57 requires the amino acid at position number 26 to be octanoylated.

The reply filed on 1/9/2006 asserts that support for the amendment can be found at page 22, lines 19-27 and page 24, lines 1-9. However, these passages do not provide support for the claimed invention. While the specification provides support for a genus of fragments containing at least 10 amino acids and containing at least one contiguous amino acid from amino acids 35-117 of SEQ ID NO: 32, the specification does not specifically disclose a fragment consisting of amino acids 24-45 of SEQ ID NO: 32. Further, the specification provides support for post-translational modifications such as acylation, the specification does not literally or inherently describe the acylation of the amino acid at position number 26 of SEQ ID NO: 32. The specification does not describe the octanoylation of any protein, and thus does not describe the octanoylation of position number 26 of SEQ ID NO: 32.

Therefore, claims 55-57 are a departure from the specification and claims as originally filed.

Claims 31-34 and 52-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection.

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Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to an isolated peptide comprising the amino acid sequence coded by nucleotides 112 to 462 of SEQ ID NO: 11, which is the amino acid sequence of SEQ ID NO: 32. Claim 32 is drawn to an isolated peptide comprising the amino acid sequence of SEQ ID NO: 32.

The claims are also drawn to isolated protein fragments of the amino acid sequence of SEQ ID NO: 32. Claim 33 is drawn to a peptide comprising at least a 10 contiguous amino acid segment of the isolated amino acid sequence of SEQ ID NO: 32, wherein the contiguous amino acid segment comprising at least one contiguous amino acid from amino acids 37-117 of SEQ ID NO: 32. Claim 34 is drawn to a peptide comprising a 10-20 contiguous amino acid segment of the peptide of claim 33. Claim 52 is drawn to an isolated peptide consisting of amino acids 24-52 of SEQ ID NO: 32. Claims 53 and 54 are drawn to an isolated peptide consisting of amino acids 24-52 of SEQ ID NO: 32, wherein the amino acid at position number 26 is acylated (claim 53) or octanoylated (claim 54). Claim 55 is drawn to an isolated peptide consisting of amino acids 24-45 of SEQ ID NO: 32. Claims 56 and 57 are drawn to an isolated peptide consisting of amino acids 24-45 of SEQ ID NO: 32, wherein the amino acid at position number 26 of SEQ ID NO: 32 is acylated (claim 56) or octanoylated (claim 57).

The claims do not require the peptides to have any specific function.

Breadth of the claims: In terms of the amino acid sequence claimed, claims 31 and 32 are narrowly drawn to the amino acid sequence of SEQ ID NO: 32, and claims 52-57 are narrowly drawn to specific fragments with specific post-translational modifications.

Claims 33 and 34 are broadly drawn to any fragment of SEQ ID NO: 32 of at least 10 amino acids (claim 33) or 10-20 amino acids (claim 34), as long as the fragment has one amino acid contiguous with amino acids 37-117 of SEQ ID NO: 32. All claims are broadly drawn to peptides of any function. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches the sequence of SEQ ID NO: 11, which encodes the peptide of SEQ ID NO: 32. The peptide of SEQ ID NO: 32 is a naturally occurring splice variant of the Ghrelin gene (e.g. page 4, lines 4-13). The peptide of SEQ ID NO: 32 differs from wild-type Ghrelin in that it contains alternative 70 amino acids from position 35 in the wild type protein, creating a variant with 117 amino acids (e.g. Table 1).

The only disclosed uses for the claimed peptides are (i) the treatment of obesity and/or diabetes (e.g. pages 50-51), and (ii) the production of antibodies for diagnostic or therapeutic purposes (e.g. page 52). The specification asserts that the amino acid sequence of SEQ ID NO: 32 is encoded by SEQ ID NO: 11, which is an “obesity and/or diabetes nucleic acid sequence.” While the specification asserts that the polypeptide of SEQ ID NO: 32 (i.e. Ghrelin Variant 2) can be used to treat diabetes and/or obesity, the relationship between Ghrelin Variant 2 and diabetes and/or obesity is not clearly taught in the specification. The specification asserts that antibodies can be used to diagnose conditions characterized by expression of the novel variant by

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over or under expression or by changes in the proportion between different splice variants (e.g. pages 54-55). Further, the specification envisions using the antibodies to block or decrease the activity of the gene product to result in a therapeutic effect (e.g. page 55, lines 25-29). There are no working examples in the present specification, and the specification does not teach a therapeutic outcome for any disease, such as diabetes or obesity, upon administration of a Ghrelin Variant 2 peptide, fragment thereof, or antibody thereto.

Predictability and state of the art: Wild type, rat ghrelin was discovered in 1999 by screening extracts from multiple tissues for their ability to bind to and activate the rat growth hormone secretagogue (GHS) receptor expressed in Chinese hamster ovary cells (Root et al, Current Drug Targets-Immune, Endocrine & Metabolic Disorders, Vol. 2, pages 27-52, 2002; e.g. page 42, Ghrelin). The active factor was identified as a 28 amino acid peptide, which was octanoylated on the third serine. Subsequently, a 117 amino acid prohormone, which is processed to an active 28 amino acid sequence, was identified in humans (Root et al, e.g. page 42, Ghrelin; Figure 7). Human and rat ghrelin differ only at two amino acid sites (Root et al, e.g. page 42, Ghrelin). Shortly after the discovery of human ghrelin, structure-function studies were performed to identify derivatives of ghrelin capable of activating growth hormone secretagogue receptor 1a (Bednarek et al, J. Med. Chem. Vol. 43, pages 4370-4376, 2000). All of the active fragments disclosed by Bednarek et al that are fragments identical to a contiguous stretch of amino acids of instant SEQ ID NO: 32 correspond to regions within amino acids 24-35 of SEQ ID NO: 32. No fragments within amino acids 37-117 are disclosed as being active. Furthermore, Root et al teach that the function of the carboxyl sequence is uncharacterized (e.g.

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page 42, Ghrelin). Thus, the claims encompass peptides that have no art-recognized activity, including peptides consisting of amino acids 24-52 and 24-45.

Wild type ghrelin is known to have effects on gastro-entero-pancreatic actions. The administration of wild type ghrelin to humans has resulted in hyperglycemia followed by reduced insulin secretion (Muccioli et al, European Journal of Pharmacology, Vol. 440, pages 235-254, 2002; e.g. page 241, section 5.1). These effects are the opposite of what one would want to induce for the treatment of diabetes, which suggests ghrelin antagonism as a potential method of therapy. While the action of ghrelin can mimic some aspects of diabetes, it is not clear that the levels of wild type ghrelin could be used to diagnose diabetes. Wu et al (Annals of Surgery, Vol. 239, No. 4, pages 464-474, 2004) teach that the suppressive actions of ghrelin on pancreatic exocrine secretion are indirect in nature, requiring not yet identified factor(s) (e.g. paragraph bridging pages 468-469). Further, ghrelin has been shown to have orexigenic activity in rodents, which cannot be recapitulated in humans (Muccioli et al, page 246, right column, 1st paragraph). Moreover, it is recognized in the art that the usefulness of ghrelin or ghrelin analogs for treating any disease is underdeveloped (Muccioli et al, e.g. page 249, right column, 1st full paragraph; Broglio et al, Treat. Endocrinol. Vol. 2, No. 3, pages 153-163, 2002, e.g. page 160, Conclusion).

With regard to diagnostic applications, decreased levels of ghrelin have been correlated with chronic obesity and acute (overfeeding) states of positive energy balance, and increased levels have been correlated with fasting states and anorexia nervosa (Broglio et al, e.g. pages 157-158, section 4.1).

Despite the development of knowledge with regard to the function of wild type ghrelin in energy balance and pancreatic function, no studies have been performed that clearly demonstrate the predictive value of a diagnostic assay for diabetes or obesity. Further, potential therapeutic results obtained in rodents have not been duplicated in humans. Moreover, the effects seen in humans suggest the development of antagonists of ghrelin for therapeutic purposes, yet there is no art of record that teaches a therapeutic effect of an anti-ghrelin antibody. Thus, it would be highly unpredictable to use a novel ghrelin peptide, which significantly differs in sequence from any known ghrelin protein (wild type human and rat ghrelin are more closely related than the two human ghrelin variants), in any diagnostic or therapeutic method for diabetes and/or obesity. Because the role of the claimed peptides and fragments in diabetes and obesity in humans is not known, it would be unpredictable to use any antibody to any claimed peptide of the ghrelin variant.

Amount of experimentation necessary: The quantity of experimentation necessary to use even one of claimed peptides for the diagnosis or treatment of diabetes and/or obesity is high, as the skilled artisan could not rely on the prior art or present specification to teach how to use any peptide of SEQ ID NO: 32 or fragment thereof. In order to carry out the claimed invention, one would be required to perform a large amount of trial and error experimentation to determine the role of the peptide of SEQ ID NO: 32. First, one would need to conduct studies to determine what cells express the peptide. One would need to determine if the peptide is expressed in physiologically relevant tissues such that a diagnostic assay may be possible. Next, one would need to determine if the levels of ghrelin variant can be detected specifically apart from wild type ghrelin. Then studies large enough to provide statistically significant results would need to be

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performed to determine if ghrelin variant peptides are diagnostic markers of diabetes and/or obesity. If ghrelin variant peptides are not diagnostic markers of diabetes or obesity, one would need to test the peptides or antibodies thereof for clinical efficacy for the treatment of diabetes or obesity. Given the lack of correlation between the orexigenic effects in rats to an effect in humans, one would not be able to use rodents as a model system for these studies. Thus, one would have to develop an acceptable model prior to determining whether the peptide or antibody has any therapeutic effect. This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to use the claimed invention. Therefore, claims 31-34 and 52-57 are not considered to be enabled by the instant specification.

Response to Arguments

Applicant's arguments filed 11/28/2005, with respect to the rejection of claims 33 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) have been fully considered but they are not persuasive. The response essentially asserts that the specification provides support for fragments of the protein of SEQ ID NO: 32, which contain the differences between the variant and original sequences. The remarks have been fully considered, and it has been concluded that the specification provides support for fragments that comprise at least a 10 contiguous amino acid segment of the isolated amino acid

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sequence of SEQ ID NO: 32, wherein said contiguous amino acid segment comprises at least one amino acid from amino acids 35-104 of SEQ ID NO: 32. Table 1 indicates that variant ghrelin differs from wild type (original) ghrelin as having alternative 70 amino acids from position 35. The specification and claims as originally filed do not provide support for fragments comprising at least one amino acid from amino acids 37-117 of SEQ ID NO: 32.

Applicant's arguments, see pages 9-10, filed 11/28/2005, with respect to the rejection of claims 33 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement have been fully considered and are persuasive. The previous rejection of claims 33 and 34 has been withdrawn.

Conclusion

No claims are allowed.

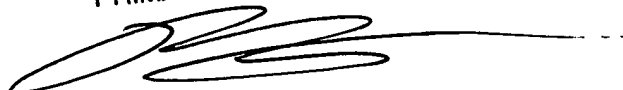
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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CELINE QIAN, PH.D.
PRIMARY EXAMINER



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Jennifer Dunston, Ph.D.
Examiner
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